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induced immune dysfunctions selected from the group consisting of including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs.

Sub  
B6

- 37. A pharmaceutical composition as claimed in claim 14 for treatment of fibromyalgia.
- 38. A pharmaceutical composition as claimed in claim 14 for treatment of anorexia or bulimia nervosa.
- 39. A pharmaceutical composition as claimed in claim 14 for treatment of cerebral ischemia, selected from the group consisting of cerebral hippocampal ischemia; excitotoxic neuronal damage.
- 40. A pharmaceutical composition as claimed in claim 14 for treatment of including social phobia, agoraphobia or specific phobias

**REMARKS**

A copy of claims 1, 2,, 3, 4, 13 and 14, showing the amendments thereto is attached as an Appendix.

A new paragraph has been inserted on page 1 to set out the applications from which benefit is claimed. This application was filed prior to November 29, 2000 so that no petition is required. In any case priority claims were made on the declaration filed on this application.

On the issue raised in paragraph 7 of the action, it is pointed out that Application Serial No 09/254387 is a U.S. national stage entry of International Patent Application PCT/IB95/00437 which was filed on June 6, 1995. Since 35 USC 363 provides that such International Application has, with one exception, "the effect of a national patent application" it is submitted that the declaration properly set out the date of June 6, 1995 as the filing date of Serial No 09/254387 and that no new declaration ids required.

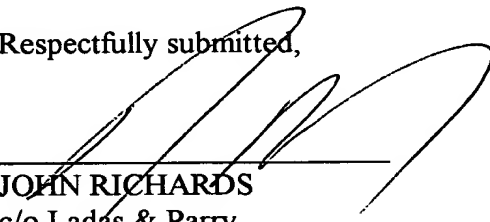
The rejections under 35 USC 112 have been met. In most cases, the corrections made are self-evident. References to Z groups and Formulae I and III have been deleted as being irrelevant to what is now claimed. So far as the use of the terms "alkyl", "alkylene", "cycloalkyl" and "cycloalkylene" including unsaturation is concerned, page 36 lines 3 to 5 make it clear that the use of these terms in the present application was in some cases intended to include unsaturated

groups. In an effort to meet the examiner's concerns, where appropriate, the term "hydrocarbyl" and its derivatives has been used to replace the terms questioned by the Examiner in those definitions where the original text makes it clear that the group in question is one where reference is made to the presence of possible double or triple bonds, namely the R<sub>1</sub> (alkyl, alkylene, cycloalkyl, cycloalkylene and heterocycloalkyl), R<sub>2</sub> (alkyl, alkylene, cycloalkyl, cycloalkylene and heterocycloalkyl), R<sub>4</sub> (alkyl and alkylene) R<sub>5</sub> alkyl and alkylene). New claim 29 is based on language that was included in claim 1 as filed as being "especial" possibilities as R<sub>24</sub> and R<sub>25</sub>.

The rejection under 35 USC 102 is respectfully traversed. As noted above, the present application claims the benefit of Application Serial No 09/254387 which has a filing date of June 6, 1995. This date is prior to the publication date of WO 95/33750. Furthermore, even if this were not the case, it is pointed out that the present applicant is the same person as the author of WO/9533750 so that it is simply not possible for this document to disclose the same invention as now claimed on a date prior to the present applicant's having made such invention.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

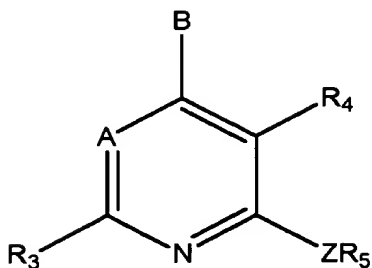
Respectfully submitted,



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## Appendix

1(Amended) A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

A is CR<sub>7</sub>;

B is -NR<sub>1</sub>R<sub>2</sub>, -CR<sub>1</sub>R<sub>2</sub>R<sub>11</sub>, -C(=CR<sub>2</sub>R<sub>12</sub>)R<sub>1</sub>, -NHCHR<sub>1</sub>R<sub>2</sub>, -OCHR<sub>1</sub>R<sub>2</sub>, -SCHR<sub>1</sub>R<sub>2</sub>, -CHR<sub>2</sub>OR<sub>1</sub>, -CHR<sub>1</sub>OR<sub>2</sub>, -CHR<sub>2</sub>SR<sub>1</sub>, -C(S)R<sub>2</sub>, -C(O)R<sub>2</sub>, -CHR<sub>2</sub>NR<sub>1</sub>R<sub>2</sub>, -CHR<sub>1</sub>NHR<sub>2</sub>, -CHR<sub>1</sub>N(CH<sub>3</sub>)R<sub>2</sub>, or -NR<sub>12</sub>NR<sub>1</sub>R<sub>2</sub>;

Y is CH or N;

Z is NH, O, S, -N(C<sub>1</sub>-C<sub>2</sub> alkyl)-, -NC(O)CF<sub>3</sub>, or -C(R<sub>13</sub>R<sub>14</sub>), -N(C<sub>1</sub>-C<sub>2</sub> alkyl)-, -NC(O)CF<sub>3</sub>, or -C(R<sub>13</sub>R<sub>14</sub>)- wherein R<sub>13</sub> and R<sub>14</sub> are each, independently, hydrogen, trifluoromethyl or methyl, or one of R<sub>13</sub> and R<sub>14</sub> is cyano and the other is hydrogen or methyl, or -C(R<sub>13</sub>R<sub>14</sub>) is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R<sub>5</sub>, which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR<sub>12</sub>, and S(O)<sub>m</sub>, and optionally comprises from one to three double bonds, and is optionally substituted with halo, C<sub>1</sub>-C<sub>4</sub> alkyl, -O(C<sub>1</sub>-C<sub>4</sub> alkyl), NH<sub>2</sub>, NHCH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, CF<sub>3</sub>, or OCF<sub>3</sub>, with the proviso that said ring does not contain any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not comprise more than two oxygen or S(O)<sub>m</sub> heterologous members;

R<sub>1</sub> is C(O)H, C(O)(C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl), C(O)(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), C(O)(C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), C(O)(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), -C(O)(C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl, C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl, -(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), -(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene

cyclohydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), or -O-aryl, or -O-(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)-aryl; wherein said aryl, C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl, C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl, C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene, and C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R<sub>8</sub> independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl, hydroxy, chloro, bromo, iodo, CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl), -O-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), -O-CO-(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -O-CO-NH(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -O-CO-N(R<sub>24</sub>)(R<sub>25</sub>), -N(R<sub>24</sub>)(R<sub>25</sub>), -S(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -S(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl) -N(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl)CO(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -NHCO(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -COO(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -CONH(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), -CONC<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl(C<sub>1</sub>-C<sub>2</sub> alkyl hydrocarbyl), CN, NO<sub>2</sub>, -OSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl), S<sup>+</sup>(C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl)(C<sub>1</sub>-C<sub>2</sub> alkyl hydrocarbyl), -SO(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl) and -SO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl); and wherein the C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl, C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene, C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl, C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene, and C<sub>5</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl moieties of R<sub>1</sub> may optionally independently contain from one to three double or triple bonds; and wherein the C<sub>1</sub>-C<sub>4</sub> alkyl hydrocarbyl moieties and C<sub>1</sub>-C<sub>6</sub> alkyl hydrocarbyl moieties of R<sub>8</sub> can optionally independently be substituted with hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, -CH<sub>2</sub>-aryl, C<sub>3</sub>-C<sub>5</sub> cycloalkyl, or -O-(C<sub>1</sub>-C<sub>4</sub> alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl heterocyclohydrocarbyl group of R<sub>1</sub> contains from one to three heteromoieties selected from oxygen, S(O)<sub>m</sub>, nitrogen, and NR<sub>12</sub>;

R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl hydrocarbyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl, C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl, -(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl cyclohydrocarbyl), -(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkylene cyclohydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl heterocyclohydrocarbyl), aryl, -(C<sub>1</sub>-C<sub>6</sub> alkylene hydrocarbylene)aryl, or -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene cyclohydrocarbylene)(aryl); wherein each of the foregoing R<sub>2</sub> groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C<sub>1</sub>-C<sub>6</sub> alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-CO-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), -S(C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)(C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), S<sup>+</sup>(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl)I<sup>-</sup>, CN, and NO<sub>2</sub>; and

wherein the  $C_1$ - $C_{12}$  alkyl hydrocarbyl,  $-(C_1-C_6$  alkylene hydrocarbylene),  $-(C_3-C_8$  cycloalkyl),  $-(C_3-C_8$  cycloalkylene), and  $-(C_3-C_8$  heterocycloalkyl) and cyclohydrocarbyl groups of 5 - 8 carbon atoms, cyclohydrocarbylene groups of 5 to 8 carbon atoms and heterocyclohydrocarbyl groups of 5 to 8 atoms moieties of  $R_2$  may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl heterocyclohydrocarbyl group of  $R_2$  contains from one to three heteromoieties selected from oxygen,  $S(O)_m$ , nitrogen, and  $NR_{12}$ ;

or when  $R_1$  and  $R_2$  are as in  $-NHCHR_1R_2$ ,  $-OCHR_1R_2$ ,  $-SCHR_1R_2$ ,  $-CHR_1R_2$  or  $-NR_1R_2$ ,  $R_1$  and  $R_2$  of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen,  $S(O)_m$ , nitrogen or  $NR_{12}$ ; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy,  $C_1$ - $C_4$  alkyl, fluoro, chloro, bromo, iodo,  $CF_3$ ,  $-O-(C_1-C_4$  alkyl),  $-O-CO-(C_1-C_4$  alkyl),  $-O-CO-NH(C_1-C_4$  alkyl),  $-O-CO-N(C_1-C_4$  alkyl)( $C_1-C_2$  alkyl),  $-NH(C_1-C_4$  alkyl),  $-N(C_1-C_2$  alkyl)( $C_1-C_4$  alkyl),  $-S(C_1-C_4$  alkyl),  $-N(C_1-C_4$  alkyl) $CO(C_1-C_4$  alkyl),  $-NHCO(C_1-C_4$  alkyl),  $-COO(C_1-C_4$  alkyl),  $-CONH(C_1-C_4$  alkyl),  $-CON(C_1-C_4$  alkyl)( $C_1-C_2$  alkyl),  $CN$ ,  $NO_2$ ,  $-OSO_2(C_1-C_4$  alkyl),  $-SO(C_1-C_4$  alkyl), and  $-SO(C_1-C_4$  alkyl), wherein one of said one to three substituents can further be selected from phenyl;

$R_3$  is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy,  $OCF_3$ ,  $NH_2$ ,  $NH(C_1-C_2$  alkyl),  $N(CH_3)_2$ ,  $-NHCOCF_3$ ,  $-NHCH_2CF_3$ ,  $S(O)_m(C_1-C_4$  alkyl),  $CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,  $-CF_3$ , or  $CH_2OCH_3$ ;

$R_4$  is hydrogen,  $C_1$ - $C_4$  alkyl hydrocarbyl,  $C_3$ - $C_5$  cycloalkyl,  $-(C_1-C_4$  alkylene hydrocarbylene)( $C_3$ - $C_5$  cycloalkyl),  $-(C_3-C_5$  cycloalkylene)( $C_3$ - $C_6$  cycloalkyl), cyano, fluoro, chloro, bromo, iodo,  $-OR_{24}$   $C_1$ - $C_6$  alkoxy,  $-O-$  cycloalkyl,  $-O-(C_1-C_4$  alkylene hydrocarbylene)( $C_3$ - $C_5$  cycloalkyl),  $-O-(C_3-C_5$  cycloalkylene)( $C_3$ - $C_5$  cycloalkyl),  $-CH_2SC(S)O(C_1-C_4$  alkyl),  $-CH_2OF_3$ ,  $CH_2OCF_3$ ,  $CF_3$ , amino, nitro,  $-NR_{24}R_{25}$ ,  $-(C_1-C_4$  alkylene hydrocarbylene)- $OR_{24}$ ,  $-(C_1-C_4$  alkylene hydrocarbylene)Cl,  $-(C_1-C_4$  alkylene hydrocarbylene) $NR_{24}R_{25}$ ,  $-NHCOR_{24}$ ,  $-NHCONR_{24}R_{25}$ ,  $-C=NOR_{24}$ ,  $-CH=NOR_{24}$ ,  $-NHNr_{24}R_{25}$ ,  $-S(O)_mR_{24}$ ,  $-C(O)R_{24}$ ,  $-OC(O)R_{24}$ ,  $-C(O)CN$ ,  $-C(O)NR_{24}R_{25}$ ,  $-C(O)NHNr_{24}R_{25}$ , and  $-COOR_{24}$ , wherein the alkyl hydrocarbyl and alkylene hydrocarbylene groups of  $R_4$  may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents  $R_{10}$  independently selected from hydroxy, amino,  $-NHCOCH_3$ ,  $-NHCOCH_2Cl$ ,  $-NH(C_1-C_2$  alkyl),  $-N(C_1-C_2$  alkyl)( $C_1-C_2$  alkyl),  $-COO(C_1-C_4$  alkyl),  $-COOH$ ,  $-CO(C_1-C_4$  alkyl),  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_3$  thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

$R_5$  is aryl or heteroaryl and is substituted with from one to four substituents  $R_{27}$

independently selected from halo, C<sub>1</sub>-C<sub>10</sub> alkyl hydrocarbyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkylene hydrocarbylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl), C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, nitro, cyano, -NR<sub>24</sub>R<sub>25</sub>, -NR<sub>24</sub>COR<sub>25</sub>, -NR<sub>24</sub>CO<sub>2</sub>R<sub>26</sub>, -COR<sub>24</sub>, -OR<sub>25</sub>, -CONR<sub>24</sub>R<sub>25</sub>, -CO(NOR<sub>22</sub>)R<sub>23</sub>, -CON(OR<sub>22</sub>)R<sub>23</sub>, -CO<sub>2</sub>R<sub>26</sub>, -C=N(OR<sub>22</sub>)R<sub>23</sub>, and -S(O)<sub>m</sub>R<sub>23</sub>; wherein said C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (C<sub>1</sub>-C<sub>4</sub> alkylene hydrocarbylene), (C<sub>3</sub>-C<sub>8</sub> cycloalkyl), (C<sub>3</sub>-C<sub>8</sub> cycloalkylene), and (C<sub>4</sub>-C<sub>8</sub> heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (C<sub>1</sub>-C<sub>4</sub> alkylene hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), C<sub>1</sub>-C<sub>4</sub> haloalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, nitro, halo, cyano, -NR<sub>24</sub>R<sub>25</sub>, -NR<sub>24</sub>COR<sub>25</sub>, -NR<sub>24</sub>CO<sub>2</sub>R<sub>26</sub>, -COR<sub>24</sub>, -OR<sub>25</sub>, -CONR<sub>24</sub>R<sub>25</sub>, CO<sub>2</sub>R<sub>26</sub>, -CO(NOR<sub>22</sub>)R<sub>25</sub>, and -S(O)<sub>m</sub>R<sub>23</sub>; and wherein two adjacent substituents of the R<sub>5</sub> group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to -R<sup>5</sup> R<sub>5</sub>, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)<sub>m</sub>, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), C<sub>1</sub>-C<sub>4</sub> haloalkyl, nitro, halo, cyano, -NR<sub>24</sub>R<sub>25</sub>, -NR<sub>24</sub>COR<sub>25</sub>, -NR<sub>24</sub>CO<sub>2</sub>R<sub>26</sub>, -COR<sub>24</sub>, -OR<sub>25</sub>, -CONR<sub>24</sub>R<sub>25</sub>, CO<sub>2</sub>R<sub>26</sub>, -CO(NOR<sub>26</sub>)R<sub>25</sub>, or -S(O)<sub>m</sub>R<sub>23</sub>; wherein one of said one to four optional substituents R<sub>27</sub>, can further be selected from -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), SO<sub>2</sub>NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -SO<sub>2</sub>NH(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHSO<sub>2</sub>(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), and -NHSO<sub>2</sub>(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); and wherein the alkyl hydrocarbyl, and alkylene hydrocarbylene groups of R<sub>5</sub> may independently optionally contain one double or triple bond;

R<sub>7</sub> is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C<sub>1</sub> - C<sub>2</sub>)alkyl, -O(cyclopropyl), -COO(C<sub>1</sub>- C<sub>2</sub> alkyl), -COO(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -OCF<sub>3</sub>, -CF<sub>3</sub>, -CH<sub>2</sub>OH or CH<sub>2</sub>OCH<sub>3</sub>;

R<sub>11</sub> is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R<sub>12</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>22</sub> is independently at each occurrence selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), and (C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl);

R<sub>22</sub> is independently at each occurrence selected from hydrogen, C<sub>1</sub>-C<sub>14</sub> alkyl, C<sub>1</sub>-C<sub>14</sub> haloalkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), and (C<sub>1</sub>-C<sub>4</sub>) alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl);

R<sub>23</sub> is independently at each occurrence selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), aryl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

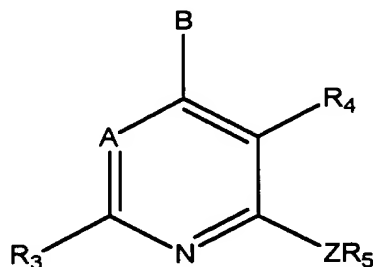
R<sub>24</sub> and R<sub>25</sub> are independently at each occurrence selected from hydrogen, -C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, ~~especially CF<sub>3</sub>-, CHF<sub>2</sub>-, CF<sub>2</sub>CF<sub>3</sub>-, or CH<sub>2</sub>CF<sub>3</sub>-~~-(C<sub>1</sub>-C<sub>4</sub> alkylene)OH, -(C<sub>1</sub>-C<sub>4</sub> alkylene)-O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkylene)-O-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -C<sub>4</sub>-C<sub>8</sub> ~~heterocycloalkyl~~ heterocyclohydrocarbyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>4</sub>-C<sub>8</sub> ~~heterocycloalkyl~~ heterocyclohydrocarbyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>4</sub>-C<sub>8</sub> ~~heterocycloalkyl~~ heterocyclohydrocarbyl), aryl, and -(C<sub>1</sub>-C<sub>4</sub> alkylene)(aryl), wherein the -C<sub>4</sub>-C<sub>8</sub> ~~heterocycloalkyl~~ heterocyclohydrocarbyl groups can each independently optionally be substituted with aryl, CH<sub>2</sub>-aryl, or C<sub>1</sub>-C<sub>4</sub> alkyl, and can optionally contain one or two double or triple bonds; or, when R<sub>24</sub> and R<sub>25</sub> are as NR<sub>24</sub>R<sub>25</sub>, -C(O)NR<sub>24</sub>R<sub>25</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkylene)NR<sub>24</sub>R<sub>25</sub>, or -NHCONR<sub>24</sub>R<sub>25</sub>, then NR<sub>24</sub>R<sub>25</sub> may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from S(O)<sub>m</sub>, oxygen, nitrogen, and NR<sub>12</sub>, and optionally containing from one to three double bonds;

R<sub>26</sub> is independently at each occurrence selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), aryl, and -(C<sub>1</sub>-C<sub>4</sub> alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that ~~heterocycloalkyl~~ heterocyclohydrocarbylene groups of the compound of formula-I, ~~H~~, or ~~H~~ do not comprise any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not comprise more than two oxygen or S(O)<sub>m</sub> heterologous members.

2. A compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is  $\text{CR}_7$ ;

B is  $-\text{NR}_1\text{R}_2$ ,  $-\text{CR}_1\text{R}_2\text{R}_{11}$ ,  $-\text{C}(=\text{CR}_2\text{R}_{12})\text{R}_1$ ,  $-\text{NHCHR}_1\text{R}_2$ ,  $-\text{OCHR}_1\text{R}_2$ ,  $-\text{SCHR}_1\text{R}_2$ ,  $-\text{CHR}_2\text{OR}_{12}$ ,  $-\text{CHR}_2\text{SR}_{12}$ ,  $-\text{C}(\text{S})\text{R}_2$  or  $-\text{C}(\text{O})\text{R}_2$ ;

Z is  $-\text{NH}$ , O, S,  $\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})$  or  $\text{C}(\text{R}_{13}\text{R}_{14})$  wherein  $\text{R}_{13}$  and  $\text{R}_{14}$  are each independently, hydrogen, trifluoromethyl or methyl or one of  $\text{R}_{13}$  and  $\text{R}_{14}$  is cyano and the other is hydrogen or methyl;

$\text{R}_1$  is  $\text{C}_1\text{-C}_6$  alkyl hydrocarbyl which may optionally be substituted with one or two substituents  $\text{R}_8$  independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo,  $\text{CF}_3$ ,  $\text{C}_1\text{-C}_4$  alkoxy,  $-\text{O-CO-}(\text{C}_1\text{-C}_4 \text{ a } \text{alkyl hydrocarbyl})$ ,  $-\text{O-CO-NH}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{O-CO-N}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})(\text{C}_1\text{-C}_2 \text{ alkyl hydrocarbyl})$ ,  $-\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{S}(\text{C}_1\text{-C}_4 \text{ alkyl})$ ,  $-\text{N}(\text{C}_1\text{-C}_4)\text{CO}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{NHCO}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{COO}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl}) \text{ alkyl hydrocarbyl}$ ,  $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ ,  $-\text{CON}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $-\text{SO}(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$  and  $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl hydrocarbyl})$ , and wherein said  $\text{C}_1\text{-C}_6$  alkyl hydrocarbyl and the  $(\text{C}_1\text{-C}_4) \text{ alkyl hydrocarbyl}$  moieties in the foregoing  $\text{R}_1$  groups may optionally contain one carbon-carbon double or triple bond;

$\text{R}_2$  is  $\text{C}_1\text{-C}_{12}$  alkyl hydrocarbyl, aryl or  $-(\text{C}_1\text{-C}_4 \text{ alkylene hydrocarbylene}) \text{ aryl}$  wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or  $-(\text{C}_1\text{-C}_6 \text{ alkylene}) \text{ cycloalkyl}$ , wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said  $-(\text{C}_1\text{-C}_6 \text{ alkylene}) \text{ cycloalkyl}$  having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by  $\text{N-R}_9$  wherein  $\text{R}_9$  is hydrogen or  $\text{C}_1\text{-C}_4$  alkyl; and wherein each of the foregoing  $\text{R}_2$  groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and  $\text{C}_1\text{-C}_4$  alkyl, or with one substituent selected from bromo, iodo,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{O-CO-}(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-\text{O-CO-N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$ ,  $-\text{S}(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $-\text{SO}(\text{C}_1\text{-C}_4 \text{ alkyl})$ , and  $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$ , and wherein said  $\text{C}_1\text{-C}_{12}$  alkyl hydrocarbyl and the  $\text{C}_1\text{-C}_4$  alkylene hydrocarbylene moiety of said  $-(\text{C}_1\text{-C}_4 \text{ alkylene hydrocarbylene}) \text{ aryl}$  may optionally contain one carbon-carbon double or triple bond;

or  $-\text{NR}_1\text{R}_2$  or  $-\text{CR}_1\text{R}_2\text{R}_{11}$  may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

$\text{R}_3$  is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy,  $\text{OCF}_3$ , methylthio, methylsulfonyl,  $\text{CH}_2\text{OH}$ , or  $\text{CH}_2\text{OCH}_3$ ;

$R_4$  is hydrogen,  $C_1$ - $C_4$  alkyl hydrocarbyl, fluoro, chloro, bromo, iodo,  $C_1$ - $C_4$  alkoxy, trifluoromethoxy,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ ,  $-CH_2CH_2OCH_3$ ,  $-CH_2OF_3$ ,  $CF_3$ , amino, nitro,  $-NH(C_1-C_4 \text{ alkyl})$ ,  $-N(CH_3)_2$ ,  $-NHCOCH_3$ ,  $-NHCONHCH_3$ ,  $-SO_n(C_1-C_4 \text{ alkyl hydrocarbyl})$  wherein  $n$  is 0, 1 or 2, cyano, hydroxy,  $-CO(C_1-C_4 \text{ alkyl hydrocarbyl})$ ,  $-CHO$ , cyano or  $-COO(C_1-C_4 \text{ alkyl})$  wherein said  $C_1$ - $C_4$  alkyl hydrocarbyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino,  $-NHCOCH_3$ ,  $-NH(C_1-C_2 \text{ alkyl})$ ,  $-N(C_1-C_2 \text{ alkyl})_2$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-CO(C_1-C_4 \text{ alkyl})$ ,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  thioalkyl, fluoro, chloro, cyano and nitro;

$R_5$  is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups  $R_5$  is substituted with from one to three substituents independently selected from fluoro, chloro,  $C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino,  $-(C_1-C_6 \text{ alkyl})O(C_1-C_6 \text{ alkyl})$ ,  $-NHCH_3$ ,  $-N(CH_3)_2$ ,  $-COOH$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-CO(C_1-C_4 \text{ alkyl})$ ,  $-SO_2NH(C_1-C_4 \text{ alkyl})$ ,  $-SO_2N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ ,  $-SO_2NH_2$ ,  $-NHSO_2(C_1-C_4 \text{ alkyl})$ ,  $-S(C_1-C_6 \text{ alkyl})$  and  $-SO_2(C_1-C_6 \text{ alkyl})$ , and wherein the  $C_1$ - $C_4$  alkyl and  $C_1$ - $C_6$  alkyl moieties of the foregoing  $R_5$  groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

$R_{11}$  is hydrogen, hydroxy, fluoro, or methoxy;

$R_{12}$  is hydrogen or  $C_1$ - $C_4$  alkyl; and

or a pharmaceutically acceptable salt of such compound.

3. (Amended) A compound according to claim 2 wherein B is  $-NR_1R_2$ ,  $-NHCHR_1R_2$ ,  $-SCHR_1R_2$  or  $-OCHR_1R_2$ ;  $R_1$  is  $C_1$ - $C_6$  alkyl hydrocarbyl, which may optionally be substituted with one hydroxy, fluoro,  $CF_3$ , or  $C_1$ - $C_2$  alkoxy group and may optionally contain one double or triple bond; and  $R_2$  is benzyl or  $C_1$ - $C_6$  alkyl hydrocarbyl which may optionally contain one carbon-carbon double or triple bond, wherein said  $C_1$ - $C_6$  alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro,  $CF_3$ ,  $C_1$ - $C_2$  alkyl, or  $C_1$ - $C_2$  alkoxy.

4. (Amended) A compound according to claim 2 wherein  $R_1$  is  $C_1$ - $C_6$  alkyl hydrocarbyl which may be substituted by fluoro,  $CF_3$ , hydroxy,  $C_1$ - $C_2$  alkyl or  $C_1$ - $C_2$  alkoxy and which may optionally contain one carbon-carbon double or triple bond.

13. (Amended) A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, ~~including but not limited to disorders induced or facilitated by CRF~~, or (b) a disorder or condition selected from inflammatory disorders ~~such as rheumatoid arthritis and osteoarthritis~~, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception ~~such as fibromyalgia~~; mood disorders ~~such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression~~, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases ~~such as Alzheimer's disease, Parkinson's disease and Huntington's disease~~; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, ~~including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs~~; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, ~~for example cerebral hippocampal ischemia; excitotoxic neuronal damage~~; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, ~~including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs~~; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13 for the treatment of a disorder selected from inflammatory disorders ~~such as rheumatoid arthritis and osteoarthritis~~, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception ~~such as fibromyalgia~~; mood disorders such as depression, ~~including major depression, single episode depression, recurrent depression, child abuse induced depression~~, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress induced headache; cancer;

irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases ~~such as Alzheimer's disease, Parkinson's disease and Huntington's disease~~; gastrointestinal diseases; eating disorders ~~such as anorexia and bulimia nervosa~~; hemorrhagic stress; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions ~~including stress induced immune dysfunctions~~; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human.